

Arsenic Exposure and Motor Function among Children in Bangladesh

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BACKGROUND: Several reports indicate that drinking water arsenic (WAs) and manganese (WMn) are associated with children's intellectual function. Very little is known, however, about possible associations with other neurologic outcomes such as motor function.

METHODS: We investigated the associations of WAs and WMn with motor function in 304 children in Bangladesh, 8–11 years of age. We measured As and Mn concentrations in drinking water, blood, urine, and toenails. We assessed motor function with the Bruininks-Oseretsky test, version 2, in four subscales—fine manual control (FMC), manual coordination (MC), body coordination (BC), and strength and agility—which can be summarized with a total motor composite score (TMC).

RESULTS: Log-transformed blood As was associated with decreases in TMC [$\beta = -3.63$; 95% confidence interval (CI): $-6.72, -0.54$; $p < 0.01$], FMC ($\beta = -1.68$; 95% CI: $-3.19, -0.18$; $p < 0.05$), and BC ($\beta = -1.61$; 95% CI: $-2.72, -0.51$; $p < 0.01$), with adjustment for sex, school attendance, head circumference, mother's intelligence, plasma ferritin, and blood Mn, lead, and selenium. Other measures of As exposure (WAs, urinary As, and toenail As) also were inversely associated with motor function scores, particularly TMC and BC. Square-transformed blood selenium was positively associated with TMC ($\beta = 3.54$; 95% CI: $1.10, 6.0$; $p < 0.01$), FMC ($\beta = 1.55$; 95% CI: $0.40, 2.70$; $p < 0.005$), and MC ($\beta = 1.57$; 95% CI: $0.60, 2.75$; $p < 0.005$) in the unadjusted models. Mn exposure was not significantly associated with motor function.

CONCLUSION: Our research demonstrates an adverse association of As exposure and a protective association of Se on motor function in children.

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Epidemiologic evidence of neurotoxicity associated with arsenic (As) exposure from occupational sources or via drinking water is well documented (Hafeman et al. 2005; Mukherjee et al. 2003; Rahman et al. 2001; Tseng et al. 2006). In the past decade, studies from China (Wang et al. 2007), Mexico (Calderon et al. 2001; Rosado et al. 2007), India (von Ehrenstein et al. 2007), and Taiwan (Tseng et al. 2006) have also demonstrated evidence of an impact on cognitive development, reflected in lower intelligence scores, deficits in long-term memory, and delayed linguistic abstraction among children exposed to As from drinking water. We previously described lower intellectual functioning among children exposed to low to moderate levels of drinking water As (WAs) in two separate studies in Bangladesh (Wasserman et al. 2004, 2007). Recent studies have also reported evidence of manganese (Mn)–induced neurotoxicity in children (Bouchard et al. 2007; Wasserman et al. 2006; Wright et al. 2006). For instance, we observed deficits in intellectual functioning among children exposed to elevated Mn in drinking water in Bangladesh (Wasserman et al. 2006), and in Korea children with higher blood Mn (BMn)

received lower intelligence test scores (Kim et al. 2009). In a small study of U.S. children living on a former mining site, those with higher hair As and Mn performed less well in cognitive tests (Wright et al. 2006).

Until now, most epidemiologic studies have focused on impaired cognitive function as a measure of neurotoxicity in children exposed to As. Other developmental outcomes, such as motor function, have largely been ignored. Several reports have noted evidence of As-induced neurotoxicity, including peripheral neuropathy, in adults (Hafeman et al. 2005; Mukherjee et al. 2003). A recent cross-sectional study of Taiwanese adolescents reported adverse associations between WAs and several measures of motor and sensory nerve peripheral conduction (Tseng et al. 2006).

In 2000, we established the Health Effects of Arsenic Longitudinal Study (HEALS) of 12,000 adults in Araihaaz, Bangladesh, and have studied subsets of their children who have naturally occurring As and Mn in their drinking water; in 2006–2008 an additional 8,000 participants were added to the cohort. In the present study, we examined whether As and Mn from drinking water were associated with motor function in 8- to 11-year-old

children. Because selenium (Se) is known to antagonize As (Levander 1977), we also measured blood Se (BSe) and examined its role in motor function among our study participants.

Materials and Methods

Participants. We obtained approval from institutional review boards at Columbia University and from the Bangladesh Medical Research Council. A detailed description of the methodology, including selection and enrollment procedures, water, and biological sample collection and processing, has been previously published (Wasserman et al. 2011). In short, our aim was to recruit 75 eligible children 8–11 years of age into each of four groups based on their home well-water concentrations: high As–high Mn (As > 10 $\mu\text{g/L}$ and Mn > 500 $\mu\text{g/L}$), high As–low Mn, low As–high Mn, and low As–low Mn.

Procedure. We used data on WAs and drinking water Mn (WMn) from our HEALS cohort central database to generate a list of 772 households with children who were potential participants. Between January and December 2008, field staff verified their current address, As and Mn status of their well water, and eligibility criteria. If parents and children were willing, and if the child was attending school in an age-appropriate class, informed parental consent and child assent were obtained. At this visit, the field team also collected sociodemographic information for the household and made an appointment for mother and child to appear at the field clinic. We continued household visits until approximately 75 children in each of the four groups had been recruited. At the

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field clinic, motor function was assessed using the Bruininks-Oseretsky test, 2nd edition (BOT-2) (Bruininks and Bruininks 2005). Biological samples (urine, blood, and toenail samples) were collected.

In total, 304 children completed assessments. Five participants were excluded from analysis because of inadequate blood samples.

Measures. Water sample collection and measurement of As and Mn. Children who had been drinking water from the same well for at least the past year were recruited. At the time of recruitment, almost all ($n = 297$, 97.7%) mothers of children in the current cohort had reported drinking exclusively from the index well, and 78% had drunk water from that well for ≥ 5 years.

Field sample collection and laboratory analyses procedures are described elsewhere in detail (Cheng et al. 2004; van Geen et al. 2005, 2007). Water samples were analyzed by high-resolution inductively coupled plasma mass spectrometry (HR-ICP-MS) as previously described (van Geen et al. 2007). The analytical detection limit of the method is 0.1 $\mu\text{g/L}$; the standard deviation of a single measurement is conservatively estimated at 4 $\mu\text{g/L}$ (van Geen et al. 2005). Mn concentrations were also determined by HR-ICP-MS. The detection limit of the method for Mn is also 0.1 $\mu\text{g/L}$, and its precision is 2% (Cheng et al. 2004).

Water samples were collected in 20-mL polyethylene scintillation vials. The samples were acidified to 1% with high-purity Optima HCl (Fisher Scientific, Pittsburgh, PA, USA) at least 48 hr before analysis (van Geen et al. 2007). Water samples are then

diluted 1:10 for As and Mn by HR-ICP-MS (Cheng et al. 2004; van Geen et al. 2005). For As, the detection limit of the method is typically $< 0.2 \mu\text{g/L}$, and the long-term reproducibility determined from consistency standards included with each run averages 4% ($1 - \sigma$) in the 40–500 $\mu\text{g/L}$ range. For Mn, the detection limit of the method is typically $< 0.02 \text{ mg/L}$, and the long-term reproducibility averages 6% in the 0.2–2.0 mg/L range.

Urine collection and urinary As and creatinine assays. Spot urine samples were collected in 50-mL acid-washed tubes and carried in portable coolers with ice packs for up to 6 hr until storage at -20°C . All samples were frozen until shipment to Columbia University on dry ice. Urinary As (UAs) assays were performed with graphite furnace atomic absorption using a PerkinElmer Analyst 600 graphite furnace system (PerkinElmer, Shelton, CT, USA) as previously described (Nixon et al. 1991). The detection limit for UAs was 2 $\mu\text{g/L}$. Urinary creatinine (UCr) was analyzed by a colorimetric method based on the Jaffe reaction.

Blood sample collection and processing. Blood samples were collected in two Vacutainers with EDTA to prevent coagulation. One vacutainer was frozen intact, whereas plasma from the other was aliquoted; all were kept at -20°C until shipment to Columbia University on dry ice.

Venous whole blood samples were analyzed for blood lead (BPb), BMn, BSe, and blood As (BAs) using a PerkinElmer Elan DRC (Dynamic Reaction Cell) II ICP-MS equipped with an AS 93+ autosampler

(PerkinElmer). ICP-MS-DRC methods for metals in whole blood were developed according to published procedures (Pruszkowski et al. 1998; Stroh 1988), with modifications for blood sample preparation as suggested by the Laboratory for ICP-MS Comparison Program, Institut National de Sante Publique du Quebec. Hemoglobin and plasma ferritin (Miles et al. 1974) were also measured.

Toenail collection and assay. Nail collection, washing, and digestion were performed using a combination of two published methods (Chen et al. 1999; Das et al. 1995). After collection, the toenail samples were thoroughly washed, dried overnight, weighed, and digested in concentrated HNO_3 . The digested nail samples, diluted to final acid volume of 10%, were analyzed for As and Mn using a PerkinElmer Elan DRC II ICP-MS equipped with an AS 93+ autosampler (PerkinElmer). An ICP-MS-DRC method for metals in nails was developed from a published method (Pruszkowski et al. 1998), with modifications and adjustments based on suggestions from the PerkinElmer application laboratory. During the period in which all samples of this study were analyzed, the intraprecision coefficient of variations for nail As (NAs) and nail Mn (NMn) in these quality control samples were 2.4 and 1.0, respectively. Interprecision coefficients of variation for the same quality control samples for As and Mn were 5.3 and 6.1, respectively.

Maternal intelligence. Maternal intelligence was measured on the Wechsler Abbreviated Scale of Intelligence (WASI; 1999). Pilot testing indicated that many

Table 1. Study participant characteristics and exposure measures by WAs and WMn distribution.

| Characteristics and exposure measures | WAs and WMn levels | | | | | <i>p</i> -Value |
|---------------------------------------|------------------------------|-----------------------------------|------------------------------------|------------------------------------|-------------------------------------|-----------------|
| | Overall (<i>n</i> = 303) | Low As–low Mn (<i>n</i> = 77) | Low As–high Mn (<i>n</i> = 74) | High As–low Mn (<i>n</i> = 73) | High As–high Mn (<i>n</i> = 79) | |
| Participants' characteristics | | | | | | |
| Male [<i>n</i> (%)] | 50.0 (151) | 61.0 (47) | 48.6 (36) | 43.8 (32) | 45.5 (36) | 0.13 |
| Child age (years) | 9.6 ± 0.7 | 9.5 ± 0.8 | 9.6 ± 0.73 | 9.8 ± 0.7 | 9.5 ± 0.8 | 0.14 |
| Month attending school | 42.0 ± 16.2 | 43.3 ± 18.52 | 42.4 ± 14.8 | 42.5 ± 14.0 | 39.8 ± 17.1 | 0.69 |
| Grade | 2.9 ± 1.2 | 3.0 ± 1.3 | 2.8 ± 1.2 | 3.0 ± 1.1 | 2.9 ± 1.2 | 0.37 |
| Head circumference (cm) | 49.3 ± 1.4 | 49.3 ± 1.2 | 49.3 ± 1.4 | 49.0 ± 1.3 | 49.7 ± 1.7 | 0.17 |
| Mother's WASI raw score | 31.0 ± 10.6 | 32.0 ± 9.7 | 30.2 ± 10.6 | 31.5 ± 10.8 | 30.2 ± 11.2 | 0.41 |
| Exposure measures | | | | | | |
| Blood (µg/L) | | | | | | |
| BAs | 4.8 ± 3.2 | 3.2 ± 1.7 | 3.4 ± 1.7 | 6.2 ± 4.2 | 6.3 ± 3.0 | < 0.0001 |
| BMn | 14.7 ± 3.7 | 14.5 ± 3.8 | 15.4 ± 4.1 | 14.3 ± 3.5 | 14.6 ± 3.2 | 0.49 |
| BSe | 104.9 ± 17.2 | 106.4 ± 16.2 | 103.6 ± 15.5 | 106.7 ± 18.0 | 103.0 ± 18.7 | 0.43 |
| BPb | 114.5 ± 37.2 | 123.9 ± 38.4 | 113.9 ± 42.4 | 100.9 ± 30.5 | 118.5 ± 33.1 | 0.0009 |
| Water (µg/L) | | | | | | |
| WAs | 43.3 ± 73.6 | 2.3 ± 2.3 | 3.3 ± 2.7 | 97.3 ± 108.8 | 70.7 ± 58.1 | < 0.0001 |
| WMn | 725.5 ± 730.5 | 202.1 ± 145.4 | 1111.1 ± 686.1 | 184.0 ± 146.1 | 1367.1 ± 692.6 | < 0.0001 |
| Urine | | | | | | |
| UAs (µg/L) | 78.0 ± 72.1 | 46.7 ± 35.8 | 52.3 ± 38.7 | 106.0 ± 93.0 | 107.0 ± 79.6 | < 0.0001 |
| UCr (mg/dL) | 35.0 ± 24.1 | 35.0 ± 25.0 | 33.7 ± 24.4 | 36.8 ± 24.9 | 34.4 ± 22.6 | 0.97 |
| UAs (µg/g creatinine) | 246.5 ± 183.9 | 149.5 ± 74.4 | 173.3 ± 111.7 | 330.5 ± 247.4 | 332.0 ± 170.4 | < 0.0001 |
| NAs (µg/g) | 5.9 ± 6.3 | 2.9 ± 2.5 | 3.0 ± 2.2 | 6.9 ± 7.0 | 10.6 ± 7.7 | < 0.0001 |
| Hemoglobin (g/dL) | 12.4 ± 0.9 | 12.7 ± 1.1 | 12.2 ± 0.8 | 12.3 ± 1.0 | 12.4 ± 0.8 | 0.002 |
| Plasma ferritin (ng/mL) | 33.4 ± 17.8 | 31.5 ± 16.8 | 32.1 ± 17.5 | 36.9 ± 18.1 | 33.1 ± 18.8 | 0.19 |

Data are mean \pm SD, except as noted.

mothers without education were unable to master the abstract nature of the Similarities and Block Design subscales; thus, only the Vocabulary and Matrix Reasoning subscales were used (for more information, see Wasserman et al. 2011).

Motor function. The Bruininks-Oseretsky test, 2nd edition (BOT-2), is an individually administered test that measures a wide range of motor skills in young persons, standardized on a U.S. nationally representative sample of > 1,500 individuals 4–21 years of age. It is the most widely used standardized measure of motor proficiency, with excellent psychometrics reliability (0.90–0.97) and validity (positive predictive value ~ 88%) (Cairney et al. 2009; Deitz et al. 2007; Rodger et al. 2003; Wang TN et al. 2009; Wilson et al. 1995). It has been used successfully in studies of individuals with developmental coordination disorder (Rodger et al. 2003; Wilson et al. 1995); scores for children with developmental coordination disorder are between one and two standard deviations below norms (Deitz et al. 2007). The BOT-2 uses a composite structure organized around both the muscle groups and the limbs involved in movement, generating four subscale scores and a summary, Total Motor Composite (TMC). The Fine Manual Control (FMC) subscale examines coordination of the hands and fingers; the Manual Coordination (MC) subscale encompasses coordination of arms and hands, especially for object manipulation; the Body Coordination (BC) subscale considers posture and balance; and the Strength and Agility (SA) subscale considers locomotion.

Test materials were translated into Bangla and then back-translated into English. Study testers were trained by an experienced psychometrician (G.A.W.). Fifty children were tested in initial feasibility studies and were not included in this analysis. Testers were blind to exposure characteristics of study participants.

Questionnaire data on covariates. During home visits, the field team collected sociodemographic information, including living conditions, maternal and paternal education and occupation, school attendance, and other potential covariates (e.g., birth order, sibship size). A general assessment of child health was assessed during the home visit, via maternal interview.

Clinical examinations, anthropometric data, and tests of mother's intelligence. A full clinical examination and history of any long-term illness was collected by a trained physician at the time of the field clinic visit. Height, weight, and head circumference were measured before the assessment of motor function. At the same visit, mother's intelligence was estimated on the WASI.

Statistical analysis. Summary statistics were calculated to describe the sample

characteristics. Chi-square tests and analysis of variance (ANOVA) were used to detect group differences in categorical and continuous variables. WAs, WMn, BAs, BMn, BPb, UAs, and UCr, were log transformed to normalize their distributions to meet assumptions of ANOVA and reduce the impact of extreme values in the linear regression analysis, whereas BSe was square transformed. Spearman correlation coefficients were used to evaluate bivariate associations among motor function subtests (FMC, MC, BC, SA), total score (TMC), and the exposure variables. We estimated associations between BAs and BMn and scores for each motor function subtest in separate linear regression models, with and without adjusting for sociodemographic characteristics and other potential confounders [sex, months of school attendance, head circumference, maternal WASI score, and plasma ferritin, based on an association with any of the four subtests or total score ($p < 0.10$)]. We also checked whether associations with BAs and BMn were altered by adjustment for BPb and BSe. When estimating associations with UAs, we used models with and without adjustment for UCr. We also examined interactions between BAs and BMn and for each measure of motor function by including multiplicative interaction terms in the models. A p -value of < 0.05 was considered statistically significant. All statistical analyses were conducted using SAS software (version 9.2; SAS Institute Inc., Cary, NC, USA).

Results

Characteristics of the study participants. We found no significant differences between the participating and nonparticipating families in the sociodemographic factors sex of the child, mother's age and educational attainment, number of living siblings, land or television ownership, duration of well use, or WAs concentration (data not shown).

We found no significant differences across the four WAs/WMn groups with regard to demographic, anthropometric, or social characteristics (Table 1). The average WAs concentration of the study participants was 43 $\mu\text{g/L}$. The average plasma ferritin and hemoglobin levels of participants were 33 ng/mL and 12.5 g/dL , respectively. Children exposed to higher WAs ($> 10 \mu\text{g/L}$) had significantly higher UAs (49.4 vs. 106.6 $\mu\text{g/L}$; $p < 0.0001$), UCr (161.2 vs. 331.3 g creatinine ; $p < 0.0001$),

BAs (3.3. vs. 6.3 $\mu\text{g/L}$; $p < 0.0001$), and NAs (3.0 vs. 8.8 $\mu\text{g/g}$; $p < 0.0001$) than did children with WAs $\leq 10 \mu\text{g/L}$. In contrast, children exposed to higher WMn ($> 500 \mu\text{g/L}$) did not have higher levels of BMn (14.5 vs. 15.0 $\mu\text{g/L}$; $p = 0.17$) but differed in NMn (27.0 vs. 33.8 $\mu\text{g/g}$; $p < 0.05$), indicating that BMn may not be a good biomarker of WMn exposure in this population. Scores on TMC and four subscales (FMC, MC, BC, and SA) did not vary significantly among the four exposure groups based on combined WAs and WMn exposures (Table 2). As expected, our study children performed lower than their U.S. agemates on all subscales.

Relationships among measures of exposure and outcomes. The various measures of As exposure (WAs, BAs, UAs, NAs) were moderately correlated with each other (r -values between 0.52 and 0.67, $p < 0.0001$; data not shown). The measures of Mn exposure were not well correlated with each other (r -values between 0.05 and 0.15; data not shown). BAs was correlated positively with BMn ($r = 0.12$, $p = 0.02$) and negatively with BSe ($r = -0.13$, $p < 0.01$). BMn was negatively associated with BSe ($r = -0.33$, $p < 0.0001$).

As expected, the motor subscales were correlated with each other (r -values between 0.27 and 0.36, all $p < 0.001$) and with total score (r -values between 0.56 and 0.77, all $p < 0.001$; data not shown).

Associations between markers of As exposure and motor function. Male sex, head circumference, duration of school attendance, and plasma ferritin levels were positively associated with TMC and, with the exception of serum ferritin, were also positively associated with one or more subtests. Maternal intelligence, measured by the WASI, was not associated with TMC or the four subtests (data not shown).

In unadjusted models, we found significant inverse associations between BAs and TMC [$\beta = -3.96$; 95% confidence interval (CI): $-7.38, -0.55$; $p < 0.01$], FMC ($\beta = -1.94$; 95% CI: $-3.55, -0.35$; $p < 0.01$), and BC ($\beta = -1.38$; 95% CI: $-2.50, -0.26$; $p < 0.01$) (Table 3). Adjusting for covariates, BAs was inversely associated with TMC ($\beta = -3.63$; 95% CI: $-6.72, -0.54$; $p < 0.01$), FMC ($\beta = -1.68$; 95% CI: $3.19, -0.18$; $p < 0.01$), and BC ($\beta = -1.61$; 95% CI: $-2.70, -0.51$; $p < 0.01$).

Table 2. BOT-2 scores (mean \pm SD) by WAs and WMn category.

| Motor function measure | WAs and WMn levels | | | | | p -Value |
|------------------------|--------------------|------------------------|-------------------------|-------------------------|--------------------------|------------|
| | Overall (n = 303) | Low As–low Mn (n = 77) | Low As–high Mn (n = 74) | High As–low Mn (n = 73) | High As–high Mn (n = 79) | |
| FMC | 42.3 \pm 8.6 | 43.7 \pm 7.6 | 42.8 \pm 9.6 | 41.7 \pm 8.8 | 41.2 \pm 8.2 | 0.26 |
| MC | 38.9 \pm 7.3 | 39.7 \pm 6.9 | 39.2 \pm 7.8 | 38.4 \pm 8.2 | 38.2 \pm 6.4 | 0.56 |
| BC | 41.3 \pm 6.0 | 42.7 \pm 5.9 | 41.2 \pm 6.0 | 41.2 \pm 6.5 | 40.0 \pm 5.7 | 0.07 |
| SA | 37.4 \pm 3.7 | 37.7 \pm 3.7 | 37.5 \pm 3.5 | 37.3 \pm 3.9 | 37.2 \pm 3.8 | 0.81 |
| TMC | 160.0 \pm 18.5 | 162.5 \pm 17.3 | 161.2 \pm 19.8 | 159.2 \pm 19.8 | 157.2 \pm 17.2 | 0.33 |

Associations between As exposure and motor function were consistent with those observed for BAs when we defined exposure based on water, urine, or nail measures (Table 4). Figure 1 illustrates inverse dose-response associations between quartiles of BAs and adjusted mean TMC, FMC, and BC scores.

Associations between BSe, BMn, and BPb and motor function. BSe was significantly positively related to TMC ($\beta = 3.54$; 95% CI: 1.10, 6.00; $p < 0.01$), FMC ($\beta = 1.55$; 95% CI: 0.40, 2.27; $p < 0.01$), and MC ($\beta = 1.57$; 95% CI: 0.60, 2.55; $p < 0.01$) in unadjusted models. The positive association between BSe and TMC ($\beta = 2.72$; 95% CI: 0.11, 5.33; $p < 0.05$), FMC ($\beta = 1.24$; 95% CI: 0.01, 2.46; $p < 0.05$), and MC ($\beta = 1.26$; 95% CI: 0.22, 2.20; $p < 0.01$) remained significant when adjusted for BAs, BMn, and BPb. In addition, the positive association between BSe and MC remained significant ($\beta = 1.02$; 95% CI: 0.40, 1.99; $p < 0.01$) when adjusting for both other exposures and sociodemographic contributors. On the other hand, we found no significant associations between BMn or BPb and motor function (data not shown). We found no interaction with As exposure variables (all p -values > 0.10).

Discussion

A primary strength of this study is the use of a well-standardized multidomain measure of children's motor functioning (Cairney et al. 2009; Deitz et al. 2007; Rodger et al. 2003; Wang TN et al. 2009; Wilson et al. 1995). In this study, we observed an adverse association between As exposure and motor function in children. We found inverse associations between markers of As exposure and overall motor function regardless of the exposure marker employed (BAs, WAs, UAs, or NAs).

In particular, As exposure was associated with decreases in FMC and BC. In contrast, increases in BSe were positively associated with manual control (MC). In addition, maternal and child characteristics showed associations in the expected directions with motor function scores, attesting to the validity of the BOT-2 in our study population. However, we observed no association between Mn exposure and motor function among children in this study.

Among children exposed to As, studies from different parts of the world have documented poorer cognitive function, reflected in poorer memory skills, slower processing speed, deficits in verbal skill, and lower IQ (Calderon et al. 2001; von Ehrenstein et al. 2007; Wang et al. 2007; Wasserman et al. 2004, 2007). Currently, however, very little information is available on the mechanism(s) of As neurotoxicity in human.

Adverse association between As and motor function. Recent animal studies have reported a dose-dependent accumulation of As in many parts of the brain, including cerebral cortex, thalamus, cerebellum, pons, striatum, basal ganglia, and pituitary (Sanchez-Pena et al. 2010; Wang Y et al. 2009). The cortex, basal ganglia, and cerebellum all play important roles in cognition, memory, language development, and control and coordination of motor function. Both biochemical and morphologic changes in brain regions that are linked to cognitive and motor performance have been reported after dietary exposure to As in animal studies (Dhar et al. 2007; Haider and Najar 2008; Mishra and Flora 2008; Rao and Avani 2004; Samuel et al. 2005; Wang Y et al. 2009). For example, oxidative injury has been found in the cerebral cortex of rats (Haider and Najar 2008; Mishra and Flora 2008), as have deficits in cerebral nitric oxide production, important for neuronal transmission

in the brain (Zarazua et al. 2006). Damage to Purkinje cells of the cerebellum has also been linked to As exposure (Dhar et al. 2007). Interestingly, an elevated level of As in cerebellar tissues has been associated with impaired performance on the Morris water maze test in mice (Wang Y et al. 2009). Taken together, these diverse findings suggest that As-induced changes in these brain regions may contribute to deficits in motor coordination.

Association between Mn and motor function. We did not detect significant associations between Mn exposure and motor function. Prior studies of Mn-related motor disturbances are based largely on occupational exposure in adults, involving lengthy periods of inhalation at very high levels (Cook et al. 1974; Roels et al. 1999). Past studies of children have linked Mn exposure to hyperactive (Bouchard et al. 2007) and classroom behavior (Khan et al. 2011), deficits in memory, poorer intellectual functioning (Bouchard et al. 2011; Menezes-Filho et al. 2011; Wasserman et al. 2006), and poorer learning (Collipp et al. 1983; Pihl and Parkes 1977).

Very little information has been available on the effects of Mn on children's motor skills, although Takser et al. (2003) observed a negative relationship between cord blood Mn levels and visual-motor tasks from the McCarthy test (McCarthy 1972) that relied on hand movement (i.e., copying block designs) in a small ($n = 63$) sample of 3-year-old boys (Takser et al. 2003). Only scant data link Mn to motor function in animal studies. Deficits in spatial memory and decreased manual dexterity have been noted in monkeys injected with manganese sulfate (Schneider et al. 2006); delayed neurodevelopment has been reported in newborn rat pups orally supplemented with Mn (Tran et al. 2002). In both cases, extrapolations to

Table 3. Estimated regression coefficients relating BAs to BOT-2 scores in models with and without adjustment for other variables [β (95% CI); $n = 299$].

| Exposure measure | FMC | MC | BC | SA | TMC |
|-------------------------------|------------------------|-----------------------|------------------------|---------------------|-----------------------------------|
| Before adjustment | | | | | |
| As ^a | -1.94 (-3.55, -0.35)** | -0.70 (-2.07, 0.66) | -1.38 (-2.50, -0.26)** | 0.07 (-0.63, 0.78) | -3.96 (-7.38, -0.55)* |
| Mn ^a | -2.93 (-7.02, 1.16) | -3.61 (-7.07, -0.16)* | -0.39 (-3.27, 2.47) | -1.37 (-3.16, 0.41) | -8.32 (-17.02, 0.39) [#] |
| Se ^b | 1.55 (0.40, 2.70)** | 1.57 (0.60, 2.55)** | 0.15 (-0.66, 0.97) | 0.26 (-0.25, 0.77) | 3.54 (1.10, 6.00)** |
| After adjustment ^c | | | | | |
| As ^a | -1.68 (-3.19, -0.18)* | -0.49 (-1.73, 0.76) | -1.61 (-2.70, -0.51)** | 0.15 (-0.57, 0.86) | -3.63 (-6.72, -0.54)* |
| Mn ^a | 1.62 (-2.53, 5.77) | 1.03 (-2.40, 4.47) | 2.03 (-0.99, 5.06) | -0.66 (-2.64, 1.31) | 4.02 (-4.52, 12.56) |
| Se ^b | 0.79 (-0.41, 1.98) | 1.02 (0.04, 1.99)* | 0.30 (-0.58, 1.66) | 0.09 (-0.48, 0.66) | 2.17 (-0.30, 4.63) [†] |

^aLog transformed. ^bSquare transformed. ^cThe adjusted variables were sex, school attendance, head circumference, mother's intelligence (WASI), plasma ferritin, BMn, BSe, and BPb. R^2 values for adjusted models for FMC, MC, BC, SA, and TMC were 0.18, 0.22, 0.12, 0.03, and 0.24, respectively. * $p < 0.05$, ** $p < 0.01$, [#] $p = 0.06$.

Table 4. Estimated regression coefficients relating measures of As exposure to BOT-2 scores [β (95% CI); $n = 299$].

| Exposure measure | FMC | MC | BC | SA | TMC |
|----------------------|-----------------------|---------------------|------------------------|---------------------|------------------------|
| WAs (μ /L) | -0.54 (-1.03, -0.05)* | -0.15 (-0.52, 0.30) | -0.43 (-0.77, -0.06)* | -0.11 (-0.28, 0.18) | -1.18 (-2.13, -0.10)* |
| UAs (μ /L) | -1.03 (-2.45, 0.39) | -0.73 (-1.89, 0.44) | -1.43 (-2.67, -0.61)* | -0.19 (-0.86, 0.48) | -3.59 (-6.50, -0.68)** |
| UAs (g creatinine/L) | -0.88 (-2.28, 0.51) | -0.76 (-1.91, 0.38) | -1.60 (-2.61, -0.60)** | -0.16 (-0.83, 0.49) | -3.42 (-6.27, -0.57)* |
| NAs (μ g/g) | -0.84 (-2.20, 0.50) | -0.68 (-1.80, 0.42) | -1.86 (-2.83, -0.89)** | -0.38 (-1.02, 0.25) | -3.77 (-6.52, -1.03)** |

The models are adjusted for sex, school attendance, head circumference, mother's intelligence (WASI), BPb, BSe, Bas, and BMn measures. Exposure values are log transformed. * $p < 0.05$, ** $p < 0.01$.

human populations are problematic because doses studied may have little or no relevance to environmental exposure levels (Schneider et al. 2006; Tran et al. 2002).

Protective association between Se and motor function. Se is an essential nutrient, and inadequate Se intake is associated with adverse health outcomes—for example, Keshan's disease (Lei et al. 2010). Increasing levels of BSe were associated with better motor function. Lower plasma Se levels have been associated with decreased motor coordination among patients with Parkinson's disease (Richwine et al. 2005; Shahar et al. 2010). In mice reared in specific-pathogen-free conditions and fed a diet high in Se, improved psychomotor function has been observed (Richwine et al. 2005). In a rat model of parkinsonism, pretreatment with sodium selenite showed evidence of a protective effect (Zafar et al. 2003). Collectively, these reports are consistent with a protective effect of Se on central nervous system functioning.

A protective role of Se in As-exposed populations has also been reported. Individuals in the HEALS cohort with higher BSe are less likely to develop As-induced skin lesions (Chen et al. 2007) and more likely to demonstrate adequate As metabolism (Pilsner et al. 2011). Earlier reports suggest antagonistic roles between As and Se (Levander 1977), such that As and Se may reduce each other's toxicity by affecting biotransformation, distribution, and excretion (Csanaky and Gregus 2003; Kenyon et al. 1997). Moreover, among arsenicosis patients in China, dietary supplementation with Se was associated with a 73% decrease in hair levels of As (Wang et al. 2001). Consistent with this body of work, we observed a significant negative correlation between BSe and BAs.

The Se content of the Bangladeshi rural diet is lower than that in the United States. Dietary

Se intake among rural Bangladeshi adults is estimated to be 17–20 µg/day based on U.S. Department of Agriculture tables for Se content in foods (Spallholz et al. 2004, 2005). In the HEALS cohort the average BSe of adults and children were 150 µg/L and 106 µg/L, respectively, comparable to those reported in developed countries (Combs 2001).

Study limitations. Study participants were healthy school children who were attending school regularly, so our findings cannot be generalized to all children, even in developing nations. Second, because no test of motor skill has been normalized in Bangladesh children, we made use of standardized motor scores that are based on U.S. norms. Village life in Bangladesh affords extensive and diverse opportunity for motor development (although activities are far less structured than in the United States), so use of U.S. norms is appropriate. The expectable associations with both socioeconomic and anthropometric markers (e.g., school attendance, head circumference) in this population provide support for our use of standardized scores.

Public health importance. Although children whose motor difficulties are severe enough to warrant a diagnosis of developmental coordination disorder (American Psychiatric Association 1994) obviously face challenges in home and school settings, three studies have found functional difficulties in children whose motor problems are less marked (Dewey et al. 2002; Rodger et al. 2003; Wang TN et al. 2009). We did not assess whether children with lower motor scores faced functional limitations in their daily activities at home or school, although the FMC subscale includes items such as cutting, mazes, and figure copying and was particularly affected by As exposure. These tasks may be assumed to affect aspects of functioning in the school setting.

Conclusions

By design, half of the children in the study were consuming water with As lower than the World Health Organization recommended cutoff (< 10 µg/L). Our research demonstrates that exposure to As in drinking water at relatively low concentrations is related to children's lower scores on a standardized test of motor skill. We also demonstrated a possible beneficial role of Se in this population. Our findings add a new sense of urgency to mitigate As exposures around the world.

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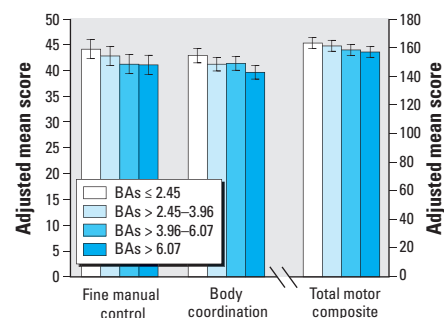


Figure 1. Covariate-adjusted mean scores by BAs quartiles for FMC, BC, and TMC scores. Models were adjusted for school attendance, head circumference, mother's intelligence (WASI), plasma ferritin, BPb, BSe, and BMn. Significance levels: FMC ($p = 0.07$), BC ($p < 0.05$) and TMC ($p = 0.1$). Difference scales were used for adjusted mean scores for TMC.

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